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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/580,380	05/26/2000	Bradford W. Gibson	UCSFP001/1584.002	1111

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EXAMINER
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CLOW, LORI A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b>	<b>Application No.</b> 09/580,380	<b>Applicant(s)</b> GIBSON ET AL.	
	<b>Examiner</b> Lori A. Clow, Ph.D.	<b>Art Unit</b> 1631	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 23 June 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.  
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☒ For purposes of appeal, the proposed <sup>arguments etc</sup> amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: \_\_\_\_\_.  
 Claim(s) objected to: 24.  
 Claim(s) rejected: 1,5,8-14,21-23 and 75-77.  
 Claim(s) withdrawn from consideration: \_\_\_\_\_.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
 12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). \_\_\_\_\_.  
 13. ☐ Other: \_\_\_\_\_.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant argues that the cited references do not teach or suggest determining a tertiary structure of a protein by applying physical distance constraint information associated with cross-linking to the set of candidate three-dimensional conformations to rank and select one or more conformations. This is not persuasive, for the reasons set forth in the Office Action of 8/18/05. Lacroix et al. discloses a method for three-dimensional modeling based on chemical cross-linking and homology modeling (page 6272, column 1, Computer-Assisted Three-Dimensional Homology Modeling) wherein the EDC cross-linked protein is isolated and fragmented by proteolysis (Abstract). Lacroix et al. do not teach the cross-linkers as recited in claims 9-13 or imposing distance constraints on candidate conformations. However, Mitra et al. disclose general chemical techniques for establishing the tertiary structures of proteins based on cross-linking reagents (page 3097, Introduction, lines 1-4) such as bifunctional reagents (page 3106, column 2, Discussion, lines 12-13) which react with amines (page 3100, column 1, lines 64-65). Mitra et al. discloses reagents such as cross-linking reagents have wide application to the studies of protein structure and the said agents are important tools for biochemist and molecular biologists for protein structure determination (page 3110, column 1, lines 22-30). Therefore, Mitra et al. suggests that cross-linking reagents are applicable and important tools to determining the tertiary structure of proteins, such as the Clr serine protease of Lacroix et al. Havel et al. teach detecting spatial proximity of distant residues to reduce the range of possible conformations (page 73, Introduction). Doing so enables the "best case" effectiveness of the various kinds of information in deducing the conformation of proteins (page 74, paragraph 1).

As previously set forth in the office action of 8/18/05, the examiner maintains that one of ordinary skill in the art at the time of the instant invention would have been motivated to use the concept of Mitra et al., for general chemical techniques, to establish the tertiary structures of proteins based on cross-linking reagents (page 3097, Introduction, lines 1-4) and to use the method Lacroix et al. for determining the tertiary structure of a protein with the cross-linking reagents of Mitra et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method for three-dimensional modeling based on chemical cross-linking and homology modeling as taught by Lacroix et al. and use the said method with the cross-linker reagents as taught Mitra et al. Mitra states that his technique has "wide applications in the area of protein subunits, multienzyme complexes, and protein structure" (page 3110, last paragraph) thus motivating one to combine this method with the method of protein structure determination of Lacroix.

It would further have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the crosslinking methods of Lacroix with the chemical techniques of Mitra in the method of Havel. One would have been motivated to do so per the statement of Havel at page 73, which states "a third major avenue detects the spatial proximity of sequentially distant residues (by disulfide bridge determination, crosslinking studies, and nmr)". Further, this enables the "best case" effectiveness of the various kinds of information in deducing the conformation of proteins (page 74, paragraph 1). For these reasons and those previously set forth, the rejection is maintained.

*For H. Claw*  
7/8/06

MARJORIE A. MORAN  
PRIMARY EXAMINER

*Marjorie A. Moran*  
7/10/06